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Retrogradely transported siRNA silences human mutant SOD1 in spinal cord motor neurons

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Abstract

The transgenic mouse model of familial amyotrophic lateral sclerosis (ALS) expressing human mutant (G93A) copper/zinc superoxide dismutase (SOD1) is an attractive model for studying the therapeutic effects of RNA interference (RNAi) because of the specific silencing of the mutant gene expression. We studied small interfering RNA (siRNA)-mediated down-regulation of human mutant G93A SOD1 gene in lumbar spinal cord of ALS mice. siRNA was applied onto the proximal nerve stump of severed sciatic nerves. One day after surgery the lumbar spinal cords were processed for RT-PCR examination. Treatment with specific siRNA resulted in 48% decrease in human SOD1 mRNA levels in lumbar spinal cord, but had no effect on the abundance of mouse ChAT and SNAP25 mRNAs which were used as randomly selected internal controls, the mark of a specific silencing of SOD1. Our findings demonstrate for the first time that siRNA, targeting mutant human SOD1 mRNA, is taken up by the sciatic nerve, retrogradely transported to the perikarya of motor neurons, and inhibits mutant SOD1 mRNA in G93A transgenic ALS mice. © 2009 Springer-Verlag.

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Keywords

G93A substitution, Amyotrophic lateral sclerosis (ALS), Lumbar spinal cord, RNA interference (RNAi), Small interfering RNA (siRNA), Superoxide dismutase-1 (SOD1)